REMARKS

Claims 44-52 are active in the case. Undersigned counsel thanks Examiner Jiang for an interview held on July 26, 2004, which is summarized below.

Support for the Amendments

Claim 44 is supported as follows: a solid composition weight of about 4,350 mg (Example 3: see the table from the Rohrich Declaration reproduced below, and specification page 16, ¶0061) to about 6,000 mg (page 13, ¶0045);

an acid component selected from citric acid and monosodium citrate (Example 3, specification page 16, ¶0061);

an acid component content of about 51 – 52 wt.% (Examples 3 to 5 of the specification; see the table from the Rohrich Declaration reproduced below. Ex. 3 – acid component 420 + 1820 = 2240/4350 = 51.49 % (rounded to 51 %); Ex. 4 – acid component 525 + 1820 = 2,345/ 4500 = 52.1 % (rounded to 52 %). (See also the original examples),

an alkaline component content of about 34 – 38 wt.% (Examples 3 to 5 of the specification: see the table from the Rohrich Declaration reproduced below. Ex. 4 – 800 + 695 + 40 = 1535/4500 = 34.1 % (rounded to 34 %); Ex. 3 – 800 + 695 + 160 = 1655/4350 = 38 %. (See also the original examples),

a solubilizing agent (specification page 9, ¶0034)

Claim 48: page 13, ¶45 (total weight of about 6,000 mg).

35 USC 112, 1st paragraph

Claims 44 - 52 are rejected under 35 USC 112, 1st paragraph, on new matter grounds. The claims have been amended to track the compositions of claims 3 – 5 of thespecification and do not contain any new matter.

Rejections over Prior Art

The present invention relates to an osteoporosis treatment using effervescent bisphosphonate compositions having a selected pH of 4.5 to about 5.5, and very high buffering capacity, causing the stomach to rapidly eject the effervescent solution. The Examiner responded to the previous amendment by pointing out that the claims were not commensurate in

scope with the examples in respect to in the combined critical range of pH and high buffering capacity. Accordingly, the claims have been amended to closely track the compositions of Examples 3, 4 and 5. This amendment also places the lower limit of quantity of buffering system further from the prior art, at 4.35 grams vs. 3.36 grams.

The applicants have recognized that a buffered, low pH environment inhibits acid rebound (the natural process of acid secretion that occurs whenever food enters the stomach), and that a large quantity of the buffer system (now 4.35 grams or more total weight) causes the stomach to eject the effervescent solution quickly. This combination reduces the esophageal irritation often seen with bisphosphonates. (Hayward Declaration ¶7)

Claims 44-52 are rejected under 35 USC 103(a) as being obvious over Katdare et al. (US 5,853,759).

Katdare et al. teaches generically that bisphosphonates can be administered in effervescent solution. but did not recognize that it isn't enough to merely dissolve the bisphosphonate in an effervescent system, or that a relatively large amount of buffering reagents promotes rapid ejection of the effervescent solution from the stomach, and so helps prevent gastric irritation. As amended, the claims recite compositions having a large amount of the buffering system (4.35 to about 6 grams total weight, with a relatively high minimum percentage of acid), at a specific pH range of 4.5 to about 5.5. This combination of pH and buffering capacity is not disclosed by Katdare et al., nor are the benefits of it suggested by the reference.

Table 1 of the Rohrich Declaration is reproduced below. It shows that the Katdare et al. examples typically have a pH of 6.1 or more. This high pH would be expected to promote acid secretion by the stomach due to the acid rebound effect, and would not be optimal for administering bisphosphonates. (Hayward Declaration ¶9)

The pH of Katdare et al.'s Example 1 is lower at 4.3, but its acid neutralizing capacity (ANC) is also very low, only 2.95 mEq of acid per dose. That is because it contains very little of the acid and alkaline components; just enough to dissolve the solids, but not enough to provide significant acid neutralizing capacity. The Katdare et al. formulas all have very low total weights of about 1.1 - 2.5 grams, compared to 4.35 - 6 grams in the present invention. The small quantities of the effervescing system in Katdare et al. would not promote rapid ejection of the bubbling solution from the stomach, and so would be prone to cause more irritation for that reason as well. (Hayward Declaration ¶11).

In summary, Katdare et al. does not disclose the claimed compositions, and does not suggest increasing the amount of acid or alkaline components to provide high buffering capacity and effervescent action.

ANC of Test Formulations According to Patent Descriptions

	Invention				**US Patent 5,853,759** (Katdare et al.)				**US Patent 5,994,329**
	Example 2	Example 3	Example 4	Example 5	Example 1	Example 2	Example 3	Example 4	Example 8
Citric acid, mg	1400	420	525	475	650	590	530	600	56.3
Monosodium citrate, mg		1820	1820	1820					
Sodium bicarbonate, mg	800	800	800	800	367	850	850	1500	
Trisodiumcitrate dihydrate, mg									1500
Potassium bicarbonate, mg	694	695	695	695					
Sodium carbonate, mg	160	160	40	80	40	87		40	
Potassiumsodiumtartrate, mg		5	5	5					
Sorbitol, mg	446	450	615	625	47.5	35	190	392.5	
Total weight (dose)	3500	4350	4500	4500	1104.5	1562	1570	2532.5	1556.3
Start pH (dose in 70ml water)	5.7	5.7	5.4	5.5	4.3	6.4	6.1	6.7	6.75
ANC per dose (mEq)	12.6	17.6	14.9	15.7	2.95	9.7	7.8	16.1	6.9

Claims 44 - 52 are rejected under 35 U.S.C. 103(a) as being obvious over Daifotis et al. (US 5,994,329).

Example 8 of Daifotis et al. is a liquid bisphosphonate composition of pH 6.75 (column 19, lines 40-62), which is *not effervescent.* It contains 1500 mg trisodiumcitrate dihydrate and 56.3 mg citric acid, but no effervescencing alkaline component. The ANC per dose is only 6.9 mEq (Table of the Rohrich Declaration) due to the small quantity of buffering components. Without any carbonate or bicarbonate the solution generates no bubbles and so would not be ejected from the stomach as rapidly as the highly effervescent solutions of the present invention. Accordingly, the rejection for anticipation under 35 U.S.C. 102(b) should be withdrawn.

CONCLUSION

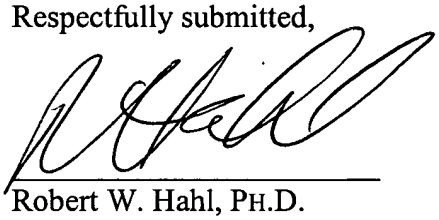
Applicants submit respectfully that the present application is in condition for allowance.

Undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3680. All correspondence should be directed to our Chicago address given below.

AUTHORIZATION

Applicants believe all fees due in connection with this filing are being paid herewith. However, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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Dated:: **August 30, 2004**

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